

Examiner Jeffrey E. Russel  
 U.S. Application Serial No. 09/873,899  
 Page 2

wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left( \sum_{i=1}^n N_i M_i \right)^2}{\sum_{i=1}^n N_i M_i^2 - \sum_{i=1}^n N_i \left( \sum_{i=1}^n N_i M_i \right)^2}$$

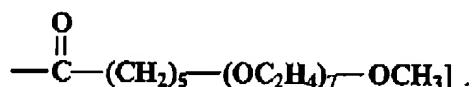
wherein:

n is the number of different molecules in the sample;

N<sub>i</sub> is the number of i<sup>th</sup> molecules in the sample; and

M<sub>i</sub> is the mass of the i<sup>th</sup> molecule.

7. (Amended) The mixture according to Claim 1, wherein the [insulin drug is human insulin and the]oligomer is covalently coupled to Lys<sup>B29</sup> of the human insulin [and has the formula:



10. (Amended) The mixture according to Claim 1, wherein the [mixture] human insulin-drug oligomer has an increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

16. (Amended) A mixture of conjugates each comprising insulin coupled to an oligomer that comprises a polyethylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left( \sum_{i=1}^n N_i M_i \right)^2}{\sum_{i=1}^n N_i M_i^2 - \sum_{i=1}^n N_i \left( \sum_{i=1}^n N_i M_i \right)^2}$$

wherein:

Examiner Jeffrey E. Russel  
U.S. Application Serial No. 09/873,899  
Page 3

n is the number of different molecules in the sample;

N<sub>i</sub> is the number of i<sup>th</sup> molecules in the sample; and

M<sub>i</sub> is the mass of the i<sup>th</sup> molecule; and

wherein the conjugate comprises a first oligomer and a second oligomer; and

[The mixture according to Claim 15]

wherein the first oligomer is covalently coupled at Lys<sup>B29</sup> of the insulin and the second oligomer is covalently coupled at N-terminal A1 or N-terminal B1 of the insulin.

18. (Amended) The mixture according to Claim [1] 16, wherein the insulin [drug] is covalently coupled to at least one of the [oligomer] oligomers by a hydrolyzable bond.

19. (Amended) The mixture according to Claim [1] 16, wherein the insulin is covalently coupled to the polyethylene glycol moiety of at least one of the [oligomer] oligomers.

20. (Amended) The mixture according to Claim [19] 16, wherein at least one of the [oligomer] oligomers [further] comprises a lipophilic moiety covalently coupled to the polyethylene glycol moiety.

21. (Amended) The mixture according to Claim [1] 16, wherein at least one of the [oligomer] oligomers [further] comprises a lipophilic moiety.

25. (Amended) The mixture according to Claim [24] 16, wherein the first and the second oligomers are the same.

26. (Amended) The mixture according to Claim [1] 16, wherein the oligomer comprises a first polyethylene glycol moiety covalently coupled to the insulin by a non-hydrolyzable bond and a second polyethylene glycol moiety covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond.

Examiner Jeffrey E. Russel  
 U.S. Application Serial No. 09/873,899  
 Page 4

28. (Amended) The mixture according to Claim [1] 16, wherein the conjugates are each amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

30. (Amended) A method of treating insulin deficiency in a subject in need of such treatment, said method comprising:

administering an effective amount of the composition of claim 29 [a mixture of conjugates each comprising an insulin drug coupled to an oligomer comprising a polyethylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where]

$$DC = \frac{\left( \sum_{i=1}^n N_i M_i \right)^2}{\sum_{i=1}^n N_i M_i^2 - \sum_{i=1}^n N_i \cdot \left( \sum_{i=1}^n N_i M_i \right)^2}$$

wherein:

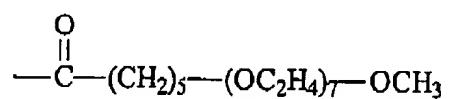
**n** is the number of different molecules in the sample;

**N<sub>i</sub>** is the number of i<sup>th</sup> molecules in the sample; and

**M<sub>i</sub>** is the mass of the i<sup>th</sup> molecule;]

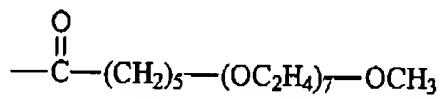
to the subject to treat the insulin deficiency.

46. (Amended) A mixture of conjugates each comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons, wherein the insulin drug is human insulin and each oligomer is covalently coupled to Lys<sup>B29</sup> of the human insulin and has the formula:

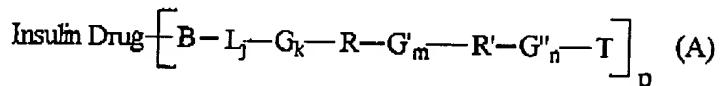


Examiner Jeffrey E. Russel  
 U.S. Application Serial No. 09/873,899  
 Page 5

50. (Amended) A mixture of conjugates each comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons, in which each conjugate[:] comprises an insulin drug coupled to an oligomer[:] and has the same number of polyethylene glycol subunits, wherein the insulin drug is human insulin and each oligomer is covalently coupled to Lys<sup>B29</sup> of the human insulin and has the formula:



52. (Amended) A mixture of conjugates in which each conjugate is the same and has the formula:



wherein:

B is carbonyl;

L is a linker moiety;

G, G' and G'' are individually selected spacer moieties;

R is C<sub>5</sub> alkylene and R' is polyethylene glycol having 7 polyethylene glycol subunits [R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety];

T is methoxy;

J[, k, m and n are individually] is 0 or 1;

k, m and n are 0; and

p is an integer from 1 to the number of nucleophilic residues on the insulin drug.

Please add the following new claims:

68. (New) The mixture according to claim 16, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 2 polyethylene glycol subunits.